REMARKS

Status of the Specification

The title has been amended for improved grammar and to specify that concentrated ritonavir compositions are objects of the present invention. Support for the "concentrated" amendment" appears, for instance, at page 11, lines 5-10 of the Specification. Support for the "ritonavir" amendment is found, for instance in original claim 21.

Status of the Claims

Claims 1-36 are pending; claims 3-5, 7, 9-14, 18, 20, and 36 have been canceled; and claims 1, 2, 6, 8, 15-17, 19, 21-35 are currently amended.

Claims 1, 2, 6, 8, 15-17, 19, 21-35 have been amended for improved grammar.

Claim 1 has been amended to recite the limitations formerly recited in canceled claims 10, 12, 13, and 14 have been added to the amended claim 1.

Claim 1 has also been amended to recite that the range of ritonavir in the claimed composition is 1.0% - 50% by weight, support for which appears in the Specification at page 11, lines 25-28.

Claim 2 has been amended to recite the limitations formerly recited in canceled claims 18 and 20.

Claim 26 has been amended so that it no longer recites the phrase, "in appropriate amounts for the composition." Claim 26 has also been amended to recite that the mixture is stirred until it "becomes a clear solution" and for improved grammar. Support for the "clear solution" amendment appears in the Specification at page 22, lines 27-29.

No new matter has been added.

1. Claims Objections:

The Examiner has objected to claims 22-25 under 37 CFR 1.75(c) as being improper form because of multiple dependent claims 18-21. (Office Action, page 2). Applicants have amended and/or canceled the claims as described above, thereby obviating the objection.

2. Claims rejections – 35 USC §112, Second Paragraph

The Examiner has rejected to claims 26-36 under 35 USC §112, Second Paragraph as allegedly indefinite for three reasons. (Office Action, pages 2-3). Applicants respectfully traverse.

First, the Examiner alleges claims 26-26 are indefinite because they "do not state a specific concentration, weight, or final product form as an endpoint." (Office Action, page2). Applicants disagree with this rejection, and point out that M.P.E.P. §2173.02 requires that an Examiner shall "allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness." *Id.* (emphasis original). Therefore, if the language of the claims can reasonably apprise one of ordinary skill in the art of the scope of the claimed invention, any rejection under 35 U.S.C. § 112, second paragraph is improper. *See id.,* §2173.05(b).

With these standards in mind, Applicants point out that the Specification discloses, without limitation, useful exemplary concentrations, weights and product forms regarding the claimed pharmaceutical compositions at page 11, line 21 to page 16, line 21, in the Examples and elsewhere. In addition, claims 1-24 make similar disclosure. Accordingly, Applicants submit that a person of ordinary skill in the art, reading the claims as a whole and in light of the teachings of the Specification, is reasonably apprised of the scope of the presently claimed processes for preparing protease inhibitor compositions.

This is especially true in light of the fact that it is well established that a patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). This is because a "... patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before." *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*: 424 F.3d 1336, 1345 (Fed. Cir. 2005) (citing *Union Oil Co. v. Atl. Richfield Co.*, 208 F.3d. 989, 997 (Fed. Cir. 2000); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995)). Accordingly, "...it is unnecessary to spell out every detail of the invention in the specification..." *Id.*

Here, Applicants further submit that a person of ordinary skill in the art of processing of pharmaceutical compositions brings a substantial amount of knowledge with him/her to the patent. This fact further demonstrates that claims 26-36 are sufficiently definite upon a fair reading of the disclosure of the present specification and claims.

For the foregoing reasons, Applicants submit claims 26-36 meet the definiteness requirement under 35 USC §112, second paragraph with respect to the concentration, weight and form of the prepared protease inhibitor compositions. Applicants respectfully request reconsideration and withdrawal of this aspect of the definiteness rejection.

Second, the Examiner has rejected claims 26-36 as allegedly indefinite for reciting the phrase, "appropriate amounts." Again, Applicants disagree with the Examiner's position, but submit that the deletion of this phrase from claim 26 obviates this aspect of the indefiniteness rejection.

Third, the Examiner has rejected claims 26-36 as allegedly indefinite for reciting the phrase, "keeping stirring until complete mixture." Here, Applicants submit that the above-described amendments to claim 26 obviate this final aspect of the Examiner's indefiniteness rejections.

In view of the foregoing remarks and claim amendments, Applicant respectfully submit that each and every aspect of the Examiner's indefiniteness rejection is traversed. Applicants therefore

request reconsideration and withdrawal of this rejection.

3. Claim rejections under 35 USC §103

3(a) Claims 1-21

The Examiner rejected claims 1-21 as allegedly unpatentable over Lipari et al. (US 6,232,333) in view of Bailey et al. (US 6,008,228). (Office Action, pages 3-7) Applicants respectfully traverse.

Applicants direct the Examiner's attention to the following remarks:

Lipari's document discloses a composition comprising ritonavir; an organic solvent including a fatty acid, preferably oleic acid; and, optionally, an alcohol mixed into the fatty acid, preferably ethanol or propylene glycol; surfactants, preferably polyoxyl castor oil or Tweens; and antioxidants, preferably butylated hydroxy toluene.

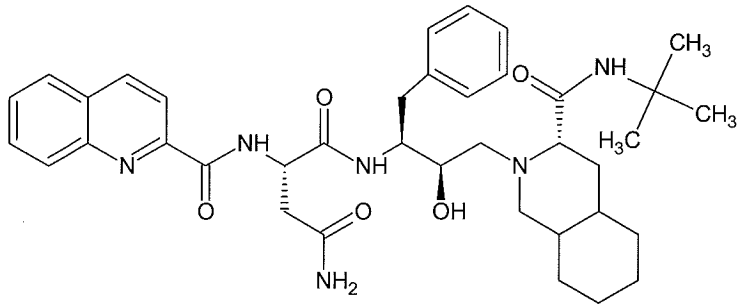
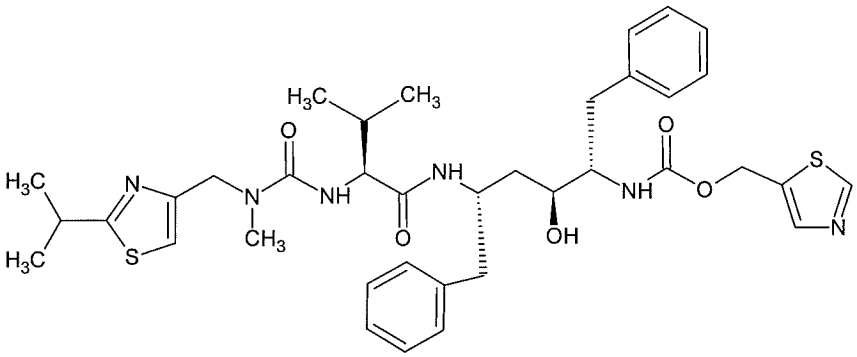
Applicants' point out that the most plentiful ingredient of Lipari's composition is the fatty acid solvent, specifically the oleic acid, which is the main component responsible for dissolution of ritonavir within the composition. It means that, in the absence of oleic acid, the Lipari's composition loses its property of suitable solubilization of ritonavir.

Turning to Bailey et al., it discloses a different composition that employs another kind of solvent to particularly dissolve saquinavir. Bailey only demonstrates enforcement for saquinavir compositions.

It is well know that the extrapolation of the use of one pharmaceutical composition for solubilizing any compound of a therapeutic class, without testing, is not possible; and, moreover, solubilization properties for various compounds within a therapeutic class are not predictable

considering the differences between the compounds and its characteristics, including physical-chemical properties.

In fact, saquinavir and ritonavir are very different molecules, thus, they present completely different properties including solubility and bioavailability.

	Saquinavir (mw: 670.85)
	Ritonavir (mw:720.955)

Protease inhibitors, especially ritonavir, are hydrophobic and lipophilic compounds, are huge molecules with high molecular weight and tend to form highly insoluble and stable crystals. As such, there are serious difficulties for obtaining adequate solvents for them, and consequently selecting an appropriate solvent that works efficiently cannot be obvious.

In spite of this well-know fact, the Examiner believes that:

> "*glycerides are derived from fatty acids, have equivalent properties, and are routinely substituted dependent on the desired physical properties of the composition.*" (Office Action, page 5).

Applicants respectfully disagree with this statement.

First of all, Lipari teaches that the fatty acids used are *liquid at room temperature* (column 8, lines 21-22), and their structures must comprise long chain of carbon atoms (C_{12}-C_{18}). On the other hand, the mixture of mono/diglycerides included in the instant invention is in the form of semi-solid liquid at room temperature and comprises medium chain of carbon atoms (C_8-C_{10}). Furthermore, glycerides are esters while fatty acids are carboxylic acids and each present distinct physical-chemical properties. In addition, because suitable solvents for dissolution of ritonavir are very scarce, to assure efficient solubilization and stabilization of the compound within the solution (or emulsion) intended for pharmaceutical purposes requires particular selection of ingredients compatible with the solvent. The skilled pharmacist knows that there are several ingredients having appropriate properties, but the efficient combination of them is not obvious. The ingredients cannot be analyzed separately, but must be analyzed in combination to produce a final composition having adequate pharmaceutical characteristics.

A pharmaceutical composition is a combination of defined elements in defined amounts and proportions, thus, the resultant product claim must be analyzed in its totality.

The following table 1 compares the main feature of the invention in question compared with the prior art documents:

Table 1: Compositions comparison.

Applicant's Invention	Lipari	Bailey
Ritonavir *Amount*: 1.0% to 60%.	Ritonavir is the only compound effectively tested in the composition, but the inventor cites other protease inhibitor agents. *Amount*: 1% to 50%.	The chemical structure of ritonavir is drawn at the specification, but this is the only citation of ritonavir in the whole document. The compound effectively tested was "compound A"[1] *Amount:* 50mg to 400 mg (preferably 200 mg – that represents 20% of saquinavir in the examples compositions).
Mixture of alcoholic solvent and alcoholic co-solvent (preferably ethanol and propylene glycol). *Amount*: 10% to 40%.	An alcohol is optionally added to the long chain fatty acid (preferably ethanol or propylene glycol). *Amount:* up to 15% (when there is mixture of ethanol and propylene glycol the amount of the total mixture is 10% (5% each) (column 11, lines 49-51 and example 35).	
C_8-C_{10} chain mono/ diglycerides. *Amount:* 20% to 80%.		At least one monoglyceride of medium chain, also can be mixture of mono/ di/ triglyceride (preferably of C_8-C_{10}. *Amount:* 40% to 80%.
Surfactant (preferably polyethoxilated castor oil 35). *Amount:* 0.1% to 20%.	Surfactant (preferably polyoxyl 35 castor oil and Tweens). *Amount:* 0% to 40%.	
Antioxidant (preferably butylated	Antioxidant (preferably butylated	Antioxidant (preferably alpha-

[1] N- tert- butyl- decahydro- 2- [2 (R)- hydroxy- 4- phenyl- 3- (S)- [[N- (2- quinolylcarbonyl)- L- asparginyl] amino] butyl]- (4aS, 8aS)- isoquinoline- 3- carboxamide. (Saquinavir)

hydroxy toluene or alpha-tocopherol). *Amount:* 0.001% to 2.0%.	hydroxy toluene). *Amount*: 0.01% to 0.08%.	tocopherol) *Amount*: 0.01% to 0.5%.
Emulsion-stabilizing agent (preferably polyethylene glycol 400). *Amount*: up to 60%.		The mono/di/triglycerides can by partially ethoxylated using polyethylene glycol (preferably PEG 300-500). *Amount:* up to 30%.
Polarity corrector agent (preferably citric or ascorbic acids). *Amount*: up to 0.5%.		
	Organic solvent: long chain fatty acid (oleic acid). *Amount*: 15% to 99%.	
		Polyvinylpyrrolidone *Amount:* up to 30%,

Table 1 shows that particular differences between the instant invention and Lipari and Bailey.

In summary, the main inventive feature of the applicant's invention is related to the "solubilizing mixture" that is comprised of a mono/diglycerides mixture, ethanol and propylene glycol. For better comparison and evidence of such inventive feature, the following Table 2 lists and compares the "solubilizing mixtures" of the invention to those of Lipari and Bailey:

Table 2: Highlighted differences among compositions.

Applicant's invention	Lipari	Bailey
C_8-C_{10} chain mono/ diglycerides. Amount: 20% to 80% + Mixture of alcoholic solvent **and** alcoholic co-solvent (preferably ethanol **and** propylene glycol) Amount: 10% to 40%	Organic solvent: long chain fatty acid (oleic acid) Amount: 15% to 99% + Optionally add an alcohol (preferably ethanol **or** propylene glycol) Amount: up to 15% PS: (when there is mixture of ethanol and propylene glycol the amount of the total mixture is 10% (5% each) (column 11, lines 49-51 and example 35)	At least one monoglyceride of medium chain, also can be mixture of mono/ di/ triglyceride (preferably of C_8-C_{10} Amount: 40% to 80%

Achieving the present invention's "solubilizing mixture" and further the composition as a whole, Applicants engaged in experimentation where potential compositions were tried but presented undesired results. Applicants submit that the non-obvious and presently claimed inventive composition results in an efficient pharmaceutical product.

In view of the foregoing points and discussion, Applicants submit that the presently claimed pharmaceutical composition is non-obvious over Lipari and Bailey, and respectfully request reconsideration and withdrawal of the obviousness rejection against claims 1-21.

3(b) Claims 26-36

The Examiner has also rejected claims 26-36 under 35 USC §103 as allegedly obvious over Lipari et al. (US 6,232,333) and Bailey et al. (US 6,008,228) in further in view of CUBolder Organic Chemistry Undergraduate Courses, Lab Techniques. Applicant respectfully traverses this rejection.

Applicants submit that a process for making new and non-obvious composition is patentable; and a process claim must be read as a whole being analyzed by all its steps and conditions and not only by some features separately.

Applicant is aware that the vacuum distillation is a common technique to reduce solvent under controlled pressure and temperature, but the special feature of the claimed process is not related only to the usage of such technique, but to the whole process itself.

The evaporation step is required for concentrating ritonavir after its dissolution to, avoid precipitation, and provides the final desired concentration of the active ingredient within the final composition.

None of the references cited by the Examiner teach nor suggest this.

Finally, Applicants direct the Examiner's attention to MPEP §2143.01, which provides that:

> "*The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination*"
>
> "*A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references*".

In view of the foregoing discussion, Applicants submit that the presently claimed process for

preparing a ritonavir pharmaceutical composition has been established as non-obvious over the prior art of record. Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection against claims 26-36.

X. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully request immedieat allowance of the claims, which define subject matter that meets all statutory patentability requirements.

Should there be any outstanding matters that need to be resolved in the present application; the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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